BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

246242

STIC-ILL

From: Lukton, David
Sent: Tuesday, March 30, 1999 2:56 PM
To: STIC-ILL

David Lukton
308-3213
AU 1654
SN 09/086327

****

El-Naggar, A.M. et al.,

"Synthesis and Biological activity of ..."

Acta Pharm. Jugosl. 35(1) 15-22 1985

[AN: 1985: 505304 HCAPLUS]

3/30
NO

D 091019

Acta Pharm. Jugosl. 35 (1985) 15—22 original scientific paper

Synthesis and biological activity of some new dibenzofuran- and 7-nitrodibenzofuran-2-sulphonylamino acid derivatives

A. M. EL-NAGGAR
A. M. ABD EL-SALAM
F. S. M. AHMED
T. M. IBRAHIM

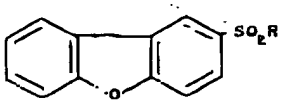
Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt

The synthesis of different dibenzofuran-2-sulphonylamino acids (*III*—*XV*), 7-nitrodibenzofuran-2-sulphonylamino acids (*XXXV*—*XLIII*), corresponding methyl esters (*XVII*—*XXIV* and *XLIV*—*XLIX*) and some dipeptide methyl ester derivatives (*XVI*, *XXV*—*XXXIV* and *LII*—*LXI*) have been achieved employing coupling of the sulphonyl chlorides (*I* and *II*) with amino acids in THF-Et_3N medium and the carbodiimide methods. Amongst the compounds synthesized, nineteen of various dibenzofuran- and 7-nitrodibenzofuran-2-sulphonylamino acid derivatives (*VI*, *VII*, *IX*, *X*, *XII*, *XVII*, *XX*, *XXI*, *XXIV*, *XXXV*, *XXXVI*, *XLI* *XLIII*, *XLIV*, *XLVIII*, *L*, *LI*, *LVII* and *LIX*) were found to possess antimicrobial activities towards different microorganisms.

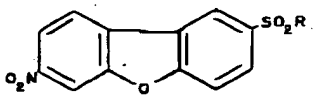
Received July 3, 1984

In previous communications (1—7), we reported the synthesis of some benzothiazoles, dibenzothiophenes, thiophene and furan, as well as other heterocyclic compounds incorporating amino acid and peptide moieties. Some of these compounds were found to display antimicrobial properties (1—7). However, the effect of replacing the dibenzothiophene moiety in these compounds by dibenzofuran and substitution in both the dibenzofuran and amino acid moieties on the antimicrobial and pharmacological activities has not yet been investigated.

This prompted the synthesis of a new class of dibenzofuran and 7-nitrodibenzofuran-2-sulphonylamino acids, methyl esters and dipeptide methyl ester derivatives (*III*—*LXI*), with a view to study the effect of different functional variants on microbiological activity.



Compounds III–XXXIV, Type-(A)



Compounds XXXV–LXI, Type-(B)

EXPERIMENTAL

All melting points are uncorrected. Thin layer chromatography (R_f values) was made on Silica-Gel-G (BDH) using benzene-ethyl acetate (1 : 1) as the solvent system and an iodine-potassium iodide (20 g/100 ml) or chlorosulphonic acid-acetic acid mixture (1 : 3) as a detection reagent. Benzidine, ninhydrin, silver nitrate and hydroxamate reactions were used for detection of the amino acid derivatives on paper chromatograms (spot reactions). The electrophoretic mobilities (E) were measured at 1000 V, 2 hours, in pyridine-acetate buffer (pH 5.6). The UV spectra (λ_{max} in nm) in ethanol solution were recorded with Unicam SP 8000, IR spectra (ν_{max} in cm^{-1}) were measured with a Unicam SP 1200 in KBr pellets and NMR data were obtained on Varian EM-360 L spectrophotometer in DMSO-d_6 and shifts are reported in (δ) ppm relative to internal TMS. Optical rotations $[\alpha]_D^{20}$ were taken in a Zeiss polarimeter with 1 dm tube, (C = 3) in the solvents (A) = acetone, (B) = DMF and (C) = = ethanol.

Dibenzofuran-2-sulphonyl chloride (I) and 7-nitrodibenzofuran-2-sulphonyl chloride (II)

I and *II* were prepared according to earlier reported procedures (8, 9).

General procedure for the synthesis of dibenzofuran-2-sulphonylamino acids (III—XV), dibenzofuran-2-sulphonyl-Gly-Gly (XVI) and 7-nitrodibenzofuran-2-sulphonylamino acids (XXXV—XLIII)

To a solution of the appropriate amino acid (0.1 mole) or Gly-Gly (0.1 mole) in water (25 ml) — THF (15 ml) mixture, was added triethylamine (5 ml) followed by dibenzofuran-2-sulphonyl chloride (*I*) or 7-nitrodibenzofuran-2-sulphonyl chloride (*II*) (0.11 mole) portion wise during 30 min. The temperature of the reaction mixture during the process of addition was kept at 10 °C and stirring continued for 45 min — 2 hours at 20 °C. Tetrahydrofuran was removed by concentration of the reaction mixture under reduced pressure and water (30 ml) added. The mixture was cooled to 0 °C and acidified with 2 mol dm^{-3} HCl, until acidic to congo red (pH 5). The crude product was filtered, washed with water and recrystallized from ethanol-water (1 : 1). All the products (*III—XVI* and *XXXV—XLIII*) were chromatographically homogeneous (detection with iodine solution, benzidine or chlorosulphonic acid-acetic acid 1 : 3 mixture) and showed negative ninhydrin reaction.

General procedure for the synthesis of dibenzofuran-2-sulphonylamino acid methyl esters (XVII—XXIV) and 7-nitrodibenzofuran-2-suliphonylamino acid methyl esters (XLIV—LI)

A suspension of dibenzofuran-2-sulphonylamino acid or 7-nitrodibenzofuran-2-sulphonylamino acid (0.01 mole) in absolute methanol (80 ml) was cooled to —10 °C and pure thionyl chloride (1.2 ml) was added dropwise during one hour. The temperature of the mixture was kept below 0 °C during the addition of thionyl chloride. The reaction mixture was then stirred for additional 3—4 hours at room temperature, kept overnight at room temperature

and the solvent was removed in vacuo. Methanol was added and reevaporated several times and the residual solid material was recrystallized from abs. methanol. The isolated methyl esters (*XVII—XXIV* and *XLIV—LI*) were chromatographically homogeneous when developed with benzidine, chlorosulphonic acid-acetic acid (1 : 3) mixture and hydroxamate reactions. *E* (for compounds *XVII—XXIV* and *XLIV—LI*) = zero.

General procedure for the synthesis of dibenzofuran-2-sulphonyl dipeptide methyl esters (XXV—XXXIV) and 7-nitrodibenzofuran-2-sulphonyl dipeptide methyl esters (LII—LXI)

To a solution of amino acid methyl ester hydrochloride (0.0082 mole) in THF (50 ml) was added triethylamine (2 ml). The solution was stirred at 20 °C for 30 min and cooled to 0 °C. The precipitated triethylamine hydrochloride was filtered off. To the filtrate at —5 °C were added dibenzofuran-2-sulphonylamino acid or 7-nitrodibenzofuran-2-sulphonylamino acid (0.008 mole) in THF (45 ml) and dicyclohexylcarbodiimide (DCC) (1.42 g) successively. The reaction mixture was stirred for 2 hours at 0 °C and for another 2 hours at 20 °C and left for 24 hours at room temperature. Dicyclohexylurea was filtered off and the filtrate was evaporated in vacuo. The residual solid was recrystallized from ethanol-water (1 : 1) mixture or abs. methanol. The products (*XXV—XXXIV* and *LII—LXI*) were easily soluble in alcohols, DMF, dioxane and insoluble in water and ether. Compounds (*XXV—XXXIV* and *LII—LXI*) were chromatographically homogeneous when detected with chlorosulphonic acid-acetic acid mixture or benzidine and gave a negative test with ninhydrin.

RESULTS AND DISCUSSION

Dibenzofuran-2-sulphonylamino acids (*III—XV*), dibenzofuran-2-sulphonyl-Gly-Gly (*XVI*) and 7-nitrobenzofuran-2-sulphonylamino acids (*XXXV—XLIII*) were readily prepared by the reaction of dibenzofuran-2-sulphonyl chloride (*I*) (8) or 7-nitrodibenzofuran-2-sulphonyl chloride (*II*) (9) with appropriate amino acid (or Gly-Gly) in water-THF-Et_3N medium. The time required for completion of the reaction (45 minutes — 2 hours) was monitored by TLC. THF was found to be the most adequate solvent for such coupling reactions. When ether, benzene or dioxane were used instead of THF, the products (*III—XVI* and *XXXV—XLIII*) were obtained in very poor (20—30%) yields and some by-products were isolated. Compounds (*III—XVI* and *XXXV—XLIII*) were chromatographically homogeneous and did not respond to ninhydrin reaction. Complete acid hydrolysis of *IV* and *XXXVI* (6 mol dm^{-3} HCl, 100 °C, 24 hours), followed by subsequent paper chromatography afforded ninhydrin positive spot of valine.

The methyl esters (*XVII—XXIV* and *XLIV—LI*) were prepared by treating the amino acid derivatives (*III—XV* and *XXXV—XLIII*) with methanol and pure thionyl chloride at —5 to —10 °C.

Table 1. Physical data of various dibenzofuran- and 7-nitrodibenzofuran-2-sulphonylamino acids, methyl esters and dipeptide methyl ester derivatives (III—LXI)

Compd.	-R	Yield** %	m.p. °C	R_f	E cm	*** $[\alpha]_D^{20}$ (C=3)	Molecular formula	Elemental analysis %					
								Calcd			Found		
								C	H	N	C	H	N
			COMPOUNDS (III—XXXIV) OF THE TYPE (A)										
III	-β-Ala	69	114—116	0.59	3.0	—	$C_{15}H_{13}NO_6S$	56.42	4.07	4.38	56.61	4.11	4.54
IV	-L-Val-	57	99—101	0.88	7.3	+22.3(A)	$C_{17}H_{17}NO_6S$	58.78	4.89	4.03	58.83	4.86	4.07
V	-DL-Val	59	217—219	0.88	7.1	—	$C_{17}H_{17}NO_6S$	58.78	4.89	4.03	59.01	4.96	4.11
VI	-L-Leu	54	180—182	0.76	8.2	+26.1(A)	$C_{18}H_{19}NO_6S$	59.83	5.26	3.87	59.82	5.31	3.85
VII	-p-Aba*	79	267—269	0.79	7.7	—	$C_{19}H_{13}NO_6S$	62.12	3.54	3.81	62.31	3.62	3.92
VIII	-m-Aba*	55	230—232	0.79	7.6	—	$C_{19}H_{13}NO_6S$	62.12	3.54	3.81	62.14	3.60	3.85
IX	-L-Phe	72	195—197	0.72	8.1	+33.7(A)	$C_{21}H_{17}NO_5S$	63.79	4.30	3.54	63.81	4.36	3.95
X	-DL-Ser	51	209—211	0.63	12.1	—	$C_{15}H_{13}NO_6S$	53.73	3.88	4.17	53.80	3.92	4.18
XI	-L-Tyr	79	120—122	0.56	2.5	+39.5(A)	$C_{21}H_{17}NO_6S$	61.31	4.13	3.40	61.40	4.16	3.44
XII	-L-Pro	66	133—135	0.61	10.8	+19.6(A)	$C_{17}H_{15}NO_5S$	59.13	4.34	4.05	59.16	4.41	4.09
XIII	-L-Trp	62	177—179	0.53	4.6	+42.8(A)	$C_{23}H_{18}N_2O_5S$	63.59	4.14	6.45	63.61	4.21	6.51
XIV	-L-Meth	49	136—138	0.80	7.7	+31.1(A)	$C_{17}H_{17}NO_5S_2$	53.82	4.48	3.69	53.66	4.52	3.71
XV	-L-Gln	64	140—142	0.74	8.2	+30.6(A)	$C_{17}H_{16}N_2O_6S$	54.25	4.25	7.44	54.33	4.31	7.51
XVI	-Gly-Gly	44	146—148	0.62	7.6	—	$C_{16}H_{14}N_2O_6S$	53.03	3.86	7.73	53.07	3.91	7.80
XVII	-β-Ala-OMe	92	128—130	0.62	0	—	$C_{16}H_{15}NO_5S$	57.62	4.50	4.20	57.69	4.55	4.27
XVIII	-L-Leu-OMe	64	151—153	0.81	0	+44.3(A)	$C_{19}H_{21}NO_5S$	60.80	5.60	3.73	60.85	5.72	3.77
XIX	-p-Aba-OMe	78	221—223	0.84	0	—	$C_{20}H_{15}NO_5S$	62.99	3.93	3.67	63.07	3.96	3.71
XX	-m-Aba-OMe	52	154—156	0.84	0	—	$C_{20}H_{15}NO_5S$	62.99	5.60	3.73	63.07	4.01	3.72
XXI	-L-Phe-OMe	81	186—188	0.85	0	+56.6(A)	$C_{22}H_{19}NO_5S$	64.54	4.64	3.42	64.62	4.75	3.48
XXII	-L-Pro-OMe	57	89—91	0.74	0	+31.4(A)	$C_{18}H_{17}NO_5S$	60.16	4.73	3.89	60.22	4.78	3.91
XXIII	-L-Tyr-OMe	84	183—185	0.57	0	+64.6(A)	$C_{22}H_{19}NO_6S$	62.11	4.47	3.29	62.19	4.51	3.32
XXIV	-L-Gln-OMe	67	166—168	0.88	0	+47 (A)	$C_{18}H_{18}N_2O_6S$	55.38	4.61	7.17	55.43	4.67	7.20
XXV	-DL-Val-DL-Val-OMe	62	173—175	0.90	0	—	$C_{23}H_{28}N_2O_6S$	60.00	6.08	6.08	60.07	6.11	6.14
XXVI	-DL-Val-L-Tyr-OMe	67	186—188	0.81	0	+59.3(A)	$C_{27}H_{28}N_2O_7S$	61.83	5.34	6.34	61.93	5.42	6.40
XXVII	-L-Pro-DL-Ser-OMe	73	80—82	0.76	0	+44.9(A)	$C_{21}H_{22}N_2O_7S$	56.50	4.93	6.27	56.55	4.99	6.31
XXVIII	-L-Pro-L-Phe-OMe	79	87—89	0.77	0	+51.9(A)	$C_{27}H_{26}N_2O_6S$	64.03	5.13	5.53	64.12	5.20	5.62
XXIX	-L-Pro-L-Tyr-OMe	81	92—94	0.77	0	+61.6(A)	$C_{27}H_{26}N_2O_7S$	62.06	4.98	5.36	62.11	5.03	5.41
XXX	-L-Phe-DL-Ser-OMe	58	171—173	0.91	0	+43.6(A)	$C_{25}H_{24}N_2O_7S$	60.48	4.83	5.64	60.53	4.91	5.71
XXXI	-L-Phe-DL-Val-OMe	54	179—181	0.94	0	+42.8(A)	$C_{27}H_{28}N_2O_6S$	63.77	5.51	5.51	63.81	5.62	5.53
XXXII	-L-Phe-L-Leu-OMe	66	175—177	0.92	0	+51.4(A)	$C_{28}H_{30}N_2O_6S$	64.36	5.74	5.36	64.43	5.82	5.41
XXXIII	-L-Phe-L-Phe-OMe	72	180—182	0.89	0	+66.1(A)	$C_{31}H_{28}N_2O_6S$	66.90	5.03	5.03	66.97	5.06	5.11
XXXIV	-L-Phe-L-Tyr-OMe	77	210—212	0.90	0	+79.2(A)	$C_{31}H_{28}N_2O_7S$	65.03	4.89	4.89	65.12	4.95	4.91

Compd.	-R	Yield** %	m.p. °C	R_f	E cm	[α]$_D^{20}$ (C=3)***	Molecular formula	Elemental analysis % Calcd C	H	N	Found C	H	N
						COMPOUNDS (XXXV—LXI) OF THE TYPE (B)							
XXXV	-β-Ala	82	119—121	0.52	4.2	—	$C_{15}H_{12}N_2O_7S$	49.45	3.39	7.69	49.56	3.36	7.70
XXXVI	-L-Val	89	245—247	0.73	9.0	+24.9(B)	$C_{17}H_{17}N_2O_7S$	52.04	4.08	7.14	52.11	4.12	7.20
XXXVII	-L-Leu	72	109—111	0.71	6.2	+27.8(B)	$C_{18}H_{16}N_2O_7S$	53.20	4.43	6.89	53.25	4.51	6.91
XXXVIII	-p-Aba	65	240—242	0.77	85	—	$C_{15}H_{12}N_2O_7S$	55.33	2.91	6.79	55.42	3.01	6.83
XXXIX	-L-Phe	75	180—182	0.81	11.3	+33.1(B)	$C_{21}H_{16}N_2O_7S$	57.27	3.63	6.36	57.31	3.70	6.30
XL	-L-Tyr	59	155—157	0.55	4.9	+41.4(B)	$C_{21}H_{16}N_2O_8S$	55.26	3.50	6.14	55.32	3.62	6.20
XLI	-L-Pro	65	207—209	0.51	7.7	+22.4(B)	$C_{17}H_{14}N_2O_7S$	52.30	3.58	7.17	52.35	3.62	7.20
XLII	-L-Trp	68	174—176	0.82	8.3	+43.6(B)	$C_{23}H_{17}N_3O_7S$	57.62	3.54	8.76	57.60	3.59	8.80
XLIII	-L-Gln	47	171—173	0.77	7.6	+29.5(B)	$C_{17}H_{15}N_3O_8S$	48.45	3.56	9.97	48.51	3.62	10.00
XLIV	-β-Ala-OMe	91	180—182	0.62	0	—	$C_{16}H_{14}N_2O_7S$	50.79	3.70	7.40	50.86	3.81	7.46
XLV	-L-Val-OMe	56	189—191	0.74	0	+29.6(C)	$C_{18}H_{18}N_2O_7S$	52.30	4.43	6.89	53.33	4.51	6.93
XLVI	-L-Leu-OMe	62	167—169	0.73	0	+33.1(C)	$C_{19}H_{20}N_2O_7S$	54.28	4.76	6.66	54.33	4.79	6.50
XLVII	-L-Phe-OMe	84	190—192	0.80	0	+37.6(C)	$C_{22}H_{18}N_2O_7S$	58.14	3.96	6.16	58.22	4.03	6.20
XLVIII	-L-Tyr-OMe	86	130—132	0.59	0	+40.2(C)	$C_{22}H_{18}N_2O_8S$	56.17	3.82	5.95	56.22	3.90	6.10
XLIX	-L-Pro-OMe	54	177—179	0.59	0	+28.1(C)	$C_{18}H_{16}N_2O_7S$	53.46	3.96	6.93	53.51	4.01	7.03
L	-L-Trp-OMe	81	209—211	0.91	0	+46.1(C)	$C_{24}H_{18}N_3O_7S$	58.41	3.85	8.51	58.45	3.92	8.63
LI	-L-Gln-OMe	65	150—152	0.82	0	+35.4(C)	$C_{18}H_{17}N_3O_8S$	48.65	3.90	9.65	49.71	3.96	9.72
LII	-L-Pro-DL-Ser-OMe	58	205—207	0.71	0	+55.1(A)	$C_{21}H_{21}N_3O_9S$	51.32	4.27	8.55	51.39	4.30	8.60
LIII	-L-Pro-DL-Val-OMe	57	120—122	0.85	0	+56.9(A)	$C_{23}H_{25}N_3O_8S$	54.87	4.97	8.34	54.93	5.01	8.30
LIV	-L-Pro-L-Tyr-OMe	77	111—113	0.92	0	+70.3(A)	$C_{27}H_{25}N_3O_8S$	57.14	4.40	7.40	57.17	4.46	7.44
LV	-L-Leu-L-Tyr-OMe	74	194—196	0.90	0	+80.2(A)	$C_{28}H_{29}N_3O_8S$	57.63	4.97	7.20	57.69	5.02	7.26
LVI	-L-Gln-DL-Ser-OMe	80	213—215	0.81	0	+44.7(A)	$C_{21}H_{22}N_4O_{10}S$	48.27	4.21	10.72	48.32	4.29	10.29
LVII	-L-Gln-L-Phe-OMe	43	197—199	0.83	0	+68.4(A)	$C_{27}H_{28}N_4O_9S$	55.67	4.46	9.62	55.72	4.59	9.70
LVIII	-L-Tyr-L-Leu-OMe	75	189—191	0.72	0	+77.3(A)	$C_{28}H_{29}N_3O_9S$	57.63	4.97	7.20	57.69	5.02	7.31
LIX	-L-Tyr-L-Phe-OMe	81	152—154	0.77	0	+85.7(A)	$C_{31}H_{27}N_3O_9S$	60.29	4.37	6.80	60.33	4.45	6.87
LX	-L-Tyr-L-Tyr-OMe	84	149—151	0.73	0	+104.2(A)	$C_{31}H_{27}N_3O_{10}S$	58.76	4.26	6.63	58.81	4.32	6.70
LXI	-L-Tyr-DL-Val-OMe	74	202—204	0.94	0	+65.5(A)	$C_{29}H_{28}N_4O_8S$	58.78	4.72	9.45	58.82	4.80	9.52

* Aba = p-Aminobenzoic acid residue.

** Crystallization solvent for compounds (III—XV, XXIV—XLIII and LIII—LXI) = ethanol-water, (XVI—XXIII and XLIV—LI) = abs. methanol.

*** Optical rotations $[\alpha]_D^{20}$ were measured (C=3) using the solvents: (A) = acetone, (B) = DMF and (C) = ethanol.

Dibenzofuran-2-sulphonyl dipeptide methyl esters (*XXV—XXXIV*) and 7-nitrodibenzofuran-2-sulphonyl-dipeptide methyl esters (*LII—LXI*) were prepared by the carbodiimide method. Coupling of dibenzofuran-2-sulphonylamino acids (*III—XV*) or 7-nitrodibenzofuran-2-sulphonylamino acids (*XXXV—XLIII*) with amino acid methyl ester hydrochlorides in THF — Et_3N medium and using the DCC technique afforded the dipeptides (*XXV—XXXIV* and *LII—LXI*). All dipeptide methyl esters (*XXV—XXXIV* and *LII—LXI*) were highly purified through repeated recrystallizations and chromatographically homogeneous materials were obtained in 43—84% yields. E = zero for all dipeptides indicating high purity of the products. Complete acid hydrolysis of (*XXVI*) (6 mol dm^{-3} HCl, 100 °C, 24 hours) afforded valine and tyrosine. Similarly, complete acid hydrolysis of (*LIX*) under the same conditions afforded tyrosine and phenylalanine. IR, UV, and NMR data confirmed the identity of all the synthesized amino acids and dipeptide derivatives. The dipeptides (*XXV—XXXIV* and *LII—LXI*) gave deep blue 1 : 1 complexes with Cu(II) λ_{max} 650—680 nm, characteristic for normal dipeptide copper(II) complexes.

The IR spectra of compounds (*III—XXIV*) showed characteristic bands at: 3320, 3180 (NH, SO_2NH); 1780, 1702 (>C=O); 1460, 1360, 1140 (SO_2NH); 2920, 1450, 1280, 1080 cm^{-1} (dibenzofuran residue) and other bands characteristic of the amino acid and dibenzofuran residues. The dipeptides (*XXV—XXXIV*) showed IR bands identical with that reported for (*III—XXIV*), and in addition the amide bands; 1650, 1550 and 1360 cm^{-1} (amide *I*, *II* and *III*), were identified. The UV spectra of compounds (*III—XXXIV*) showed λ_{max} (log ε) at 330 nm (3.10) and 267 nm (3.89) characteristic of the dibenzofuran chromophore. The NMR spectra of compounds (*III—XXXIV*) exhibited seven dibenzofuran protons in the range δ 8.5—9.4, the NH amide proton at δ 5.65 and other protons assignable to aromatic and amino acid or dipeptide residues.

The IR spectra of compounds (*XXXV—LXI*) showed characteristic bands at 3340, 3180, (NH, SO_2NH); 1780, 1720 (>C=O); 1480, 1350, 1140 (SO_2NH); 2940, 2860, 1380 cm^{-1} (NO_2) and other bands characteristic of the amino acid or dipeptide and dibenzofuran residues. The dipeptides (*LII—LXI*) showed also the IR bands characteristic of the amide bands; 1650, 1550 and 1320 cm^{-1} (amide *I*, *II* and *III*).

The UV spectra of compounds (*XXXV—LXI*) showed λ_{max} (log ε) at 332 nm (3.25) and 265 nm (3.88) characteristic of the dibenzofuran chromophore.

The NMR spectra of compounds (*XXXV—LXI*) exhibit six dibenzofuran protons in the range δ 8.5—9.3, the NH amide proton at δ 5.63 and other protons assignable to aromatic and amino acid residues.

Compounds (*III—XLI*) were prepared and characterized for the first time (cf. Table I). All the synthesized compounds (*III—LXI*) gave IR, UV and NMR spectra consistent with their assigned structures. The methods used for studying the copper(*II*) complexes were the same as described in previous papers (10, 11).

Micro-biological screening results

The antimicrobial activities of the compounds which were synthesized were tested using the hole plate and filter paper disc methods (12—16). The results were compared with the activity of the parent dibenzofuran, 7-nitrodibenzofuran, dibenzofuran-2-sulphonyl chloride (*I*) and 7-nitrodibenzofuran-2-sulphonyl chloride (*II*) which were found to be inactive against all the tested microorganisms.

In addition, the antimicrobial activity of the compounds (*III*—*LXI*) were compared with the activities of some recently synthesized dibenzothiophene derivatives (6, 7) and the results are discussed.

Dibenzofuran-2-sulphonyl-L-Leu (VI) and the corresponding -p-Aba (*VII*), *L*-Phe- (*IX*), *DL*-Ser (*X*) and *L*-Pro (*XII*) were found to possess high antimicrobial activities towards *Bacillus subtilis* (ICC-strain), *Bacillus mycoids* (USSR), *Bacillus cereus* (NRRL-B-569) and *Escherichia coli* (NRRL-B-210) with minimal inhibitory concentration (*MIC*) ranging from 50—100 μg/ml (as compared to dibenzofuran and dibenzothiophene derivatives (6, 7)), and inactive against *Salmonella typhosa* (NRRL-B-573) and *Penicillum chrysogeneum* (*MIC* 250—500 μg/ml). Dibenzofuran-2-sulphonyl-β-Ala-OMe (*XVII*) and the corresponding *m*-Aba-OMe (*XX*), *L*-Phe-OMe (*XXI*) and *L*-Gln-OMe (*XXIV*) were found to have marked growth inhibitory effect against *Bacillus subtilis*, *Bacillus mycoids* and *Bacillus cereus* (with *MIC* 25—50 μg/ml).

7-Nitrodibenzofuran-2-sulphonyl-β-Ala (*XXXV*) and the corresponding *L*-Val (*XXXVI*), *L*-Pro (*XLI*) and *L*-Gln (*XLIII*) were found to be highly active against *Bacillus subtilis*, *Bacillus cereus* and *Escherichia coli* with *MIC* ranging from 100—125 μg/ml (as compared to 7-nitrodibenzofuran, dibenzothiophene derivatives (6, 7) and *II*) and inactive against *Bacillus mycoids*, *Salmonella typhosa* and *Penicillum chrysogeneum* (*MIC* 250—500 μg/ml).

7-Nitrodibenzofuran-2-sulphonyl-β-Ala-OMe (*XLIV*) and the corresponding *L*-Tyr-OMe (*XLVIII*), *L*-Trp-OMe (*L*), *L*-Gln-OMe (*LI*), *L*-Tyr-*L*-Phe-OMe (*LIX*) and *L*-Gln-*L*-Phe-OMe (*LVII*) were found to be active against *Bacillus subtilis*, *Bacillus cereus* and *Bacillus mycoids* only (*MIC* 50—100 μg/ml).

The present investigation revealed than the introduction of sulphonyl group and nitro substituents in the 2- and 7-positions in the dibenzofuran residue in combination with amino acid moieties gave dibenzofuran-2-sulphonylamino acid derivatives of highly specific microbiological properties. The *L*-Phe, β-Ala, *L*-Pro and Gln derivatives were found to possess high antimicrobial activities when compared with the corresponding, *L*-Meth and *L*-Leu derivatives. Esterification of the terminal carboxyl group of the amino acid moieties enhance and verify the antimicrobial activities of some of the synthesized amino acid derivatives. Elongation of the peptide chain did not affect the antimicrobial activity of these compounds, since the synthesis of dibenzofuran-2-sulphonyldipeptide esters did not enhance or modify the microbiological properties of these derivatives.

A comparison of the activities of the synthesized dibenzofuran compounds with that of the microbiologically active dibenzothiophene analogues (6, 7)

showed that the dibenzofuran derivatives containing *L*-Phe, β-Ala, *L*-Pro and Gln residues possess high antimicrobial activities when compared with the corresponding dibenzothiophene derivatives. However, the dibenzothiophene derivatives containing *L*-Val, *L*-Ser and *L*-Tyr residues possess high antimicrobial properties as compared to the dibenzofuran derivatives.

Other pharmacological studies are in progress.

REFERENCES

1. A. M. El-Naggar, F. S. M. Ahmed, A. M. Abd El-Salam, B. M. Haroun, and M. S. A. Latif, *Int. J. Peptide Protein Res.* 19 (1982) 408.
2. A. M. El-Naggar, M. N. Abou El-Enein, and A. A. Makhlouf, *J. Ind. Chem. Soc.* 59 (1982) 783.
3. A. M. El-Naggar, F. S. M. Ahmed, A. M. Abd El-Salam, and S. G. Donia, *Acta. Pharm. Jugosl.* 32 (1982) 257.
4. A. M. El-Naggar, M. N. Abou El-Enein, and A. M. Makhlouf, *Bull. Soc. Chim. (Belg.)* 46 (1981) 545.
5. A. M. El-Naggar, F. S. M. Ahmed, A. M. Abd El-Salam, and S. M. El-Shami, *Egypt. J. Chem.* 26 (1983) 75.
6. A. M. El-Naggar, F. S. M. Ahmed, and S. G. Donia, *J. Ind. Chem. Soc.* 60 (1983) 479.
7. A. M. El-Naggar, F. S. M. Ahmed, and S. G. Donia, *Bull. Soc. Chim. (Beograd)* 49 (1984) 699.
8. H. Gilman, M. A. Smith, and H. J. Oalfield, *J. Amer. Chem. Soc.* 56 (1934) 1412.
9. W. Borsche and B. Schacke, *Ber.* 56 (1923) 2498 .
10. A. M. El-Naggar, M. R. Zaher, and A. M. Abd El-Salam, *J. Appl. Chem. Biotechnol* 26 (1976) 305.
11. A. M. El-Naggar, M. R. Zaher, and S. A. El-Ghaffar, *Bull. Soc. Chim. (Belg.)* 47 (1982) 253.
12. H. J. Carlson, *J. Bact.* 55 (1948) 607.
13. J. A. Epstein, *Lab. Clin. Med.* 29 (1944) 319.
14. J. G. Vincent and H. W. Vincent, *Pract. Exptl. Biol.* 55 (1944) 162.
15. G. W. Irving, *J. Bact.* 52 (1946) 10.
16. A. M. El-Naggar, F. S. M. Ahmed, M. F. Badie, and K. M. Kamel, *Int. J. Peptide. Protein. Res.* 22 (1983) 251.

SAŽETAK

Priprava i biološka aktivnost nekih novih derivata dibenzofuran- i 7-nitrodibenzofuran-2-sulfonilaminokiseline

A. M. EL-NAGGAR, A. M. ABD EL-SALAM, F. S. M. AHMED i T. M. IBRAHIM

Opisana je priprava različitih dibenzofuran-2-sulfonilaminokiselina, 7-nitrodibenzofuran-2-sulfonilaminokiselina i njihovih metilnih estera, te metilnih estera nekih dipeptidnih derivata. Korištena je reakcija sulfonil klorida s aminokiselinama i karbodiimidna metoda.

Antimikrobno djelovanje pokazuje 19 pripravljenih spojeva.